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<b>(21) International Application Number:</b> PCT/GB96/00117 <b>(22) International Filing Date:</b> 19 January 1996 (19.01.96) <b>(30) Priority Data:</b> 9501178.9 20 January 1995 (20.01.95) GB <b>(71) Applicant (for all designated States except US):</b> THE WELL-COME FOUNDATION LIMITED [GB/GB]; Unicorn House, 160 Euston Road, London NW1 2BP (GB). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> CARTER, Barry, Howard [US/US]; P.O. Box 6155, Kinston, NC 28501 (US). PARTIN, Jane, Muse [US/US]; 151 Dover Circle, Greenville, NC 27834 (US). VARLASHKIN, Peter, Gregory [US/US]; Glaxo Wellcome Inc., Intersection US 13 and State Road 1590, Greenville, NC 27835 (US). WINNIKE, Richard, Augustus [US/US]; 20 Gloucester Court, Durham, NC 27713 (US). GRUBB, William, Bayne, III [US/US]; 405 S. Eastern Street, Greenville, NC 27858 (US). CONWAY, Gregory, Alan [US/US]; Schweizerhall Inc., 3001 Hadley Road, South Plainfield, NJ 07080 (US). LAKE, Philip, George [GB/GB]; Temple Hill, Dartford, Kent DA1 5AH (GB). SKINNER, David, Michael [GB/GB]; Temple Hill, Dartford, Kent DA1 5AH	<b>(GB).</b> WHATRUP, David, James [GB/GB]; Temple Hill, Dartford, Kent DA1 5AH (GB). <b>(74) Agent:</b> MCMUNN, Watson, P.; W.H. Beck, Greener & Co., 7 Stone Buildings, Lincoln's Inn, London WC2A 3SZ (GB). <b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>	
<b>(54) Title:</b> GUANINE DERIVATIVE  <b>(57) Abstract</b>  The invention relates to an anhydrous crystalline form of (2-[2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy]ethyl L-valinate hydrochloride (otherwise known as valaciclovir hydrochloride) and a process for preparing it.		

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-1-

GUANINE DERIVATIVE

The present invention relates to a specific crystalline form of the antiviral compound valaciclovir hydrochloride, and to  
5 a process for producing it.

The compound 9-[(2-hydroxyethoxy)methyl]guanine, otherwise known as acyclovir possesses potent antiviral activity and is widely used in the treatment and prophylaxis of viral  
10 infections in humans, particularly infections caused by the herpes group of viruses (see, for example, Schaeffer et al, Nature, 272, 583-585 (1978), UK patent no. 1,523,865 and US patent no. 4,199,574). However, acyclovir is poorly absorbed from the gastrointestinal tract upon oral administration and  
15 this low bioavailability means that multiple high doses of oral drug may need to be administered, especially for the treatment of less sensitive viruses or infections in order to achieve and maintain effective anti-viral levels in the plasma.

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The L-valine ester of acyclovir, namely (2-[2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxyethyl L-valinate, (otherwise known as valaciclovir) has been shown to possess much improved bioavailability whilst retaining the anti-viral properties of  
25 acyclovir. A preferred form of this compound is its hydrochloride salt which is otherwise known as valaciclovir hydrochloride. The L-valinate ester of acyclovir and its salts including the hydrochloride salt are disclosed in US patent no. 4,957,924 (see particularly example IB), European  
30 patent no. 0308,065 (see particularly example IB) and Beauchamp et al, Antiviral Chemistry and Chemotherapy, 3(3), 157-164 (1992) (see particularly page 162 column 1).

We have now found that valaciclovir hydrochloride can exist  
35 in various forms, and moreover we have discovered a form of valaciclovir hydrochloride which is anhydrous and crystalline

and which surprisingly has particularly good pharmaceutical properties. It is particularly stable and essentially non-hygroscopic. Batches of this crystalline form can be consistently made to a high crystal form purity i.e. where the proportion of other amorphous and crystalline forms of valaciclovir hydrochloride is limited. Furthermore this anhydrous crystalline form has good storage properties and can be readily formulated into pharmaceutical compositions such as tablets and capsules.

Accordingly in a first aspect of the invention there is provided valaciclovir hydrochloride in essentially anhydrous crystalline form including substantially the following d spacing pattern (in Angstroms):

10.20  $\pm$  0.08, 8.10  $\pm$  0.06, 7.27  $\pm$  0.06, 6.08  $\pm$  0.05, 5.83  $\pm$  0.03, 5.37  $\pm$  0.02, 5.23  $\pm$  0.02, 4.89  $\pm$  0.02, 4.42  $\pm$  0.02, 4.06  $\pm$  0.02, 3.71  $\pm$  0.02, 3.39  $\pm$  0.02, 3.32  $\pm$  0.02, 2.91  $\pm$  0.02, 2.77  $\pm$  0.02.

Hereinafter by "anhydrous crystalline form" according to the invention, we mean a crystalline form having substantially the same X-ray powder diffraction pattern as shown in figures 1 to 3, or having substantially the same d spacing pattern as defined above.

Any particular crystalline form of a molecule will have its own unique d spacing pattern which can be determined from its powder X-ray diffraction pattern using the Bragg equation

$$n\lambda = 2 d \sin\theta$$

where: n is the order of diffraction (usually 1);

$\lambda$  is the wavelength of the radiation;

d is the d spacing (Angstroms); and

$\theta$  is the angle of deflection of the radiation

-3-

It will be appreciated that the measured d spacings can vary slightly e.g. depending on the degree to which the powder sample is packed.

5 The invention relates to the anhydrous crystalline form both in pure form and in admixture with other forms of valaciclovir hydrochloride such as hydrated crystalline forms. For example in any batch containing the anhydrous crystalline valaciclovir hydrochloride, there may also be hydrated crystalline forms  
10 of the compound.

Preferably the crystal form purity in any drug batch of valaciclovir hydrochloride is at least 70% w/w, more preferably at least 80% w/w, more preferably still at least  
15 90% w/w, and most preferably at least 95% of anhydrous crystalline valaciclovir hydrochloride (as defined above).

In an alternative method of determining crystal form purity, since the anhydrous crystalline form of valaciclovir hydrochloride is essentially free of water of hydration, the  
20 proportion of hydrate forms of valaciclovir hydrochloride in any batch of the compound can be measured by the overall water of hydration content of each batch.

25 Accordingly in a second aspect of the invention there is provided valaciclovir hydrochloride having a water of hydration content of not more than 3% by weight (w/w) and including substantially the X-ray powder diffraction patterns of figures 1 to 3, or substantially the same d spacing pattern  
30 shown above.

More preferably the water of hydration content is not more than 2% w/w, still more preferably not more than 1.5% w/w, and more preferably still not more than 1% w/w, and most  
35 preferably not more than 0.5% w/w.

This water of hydration content is measured by the Karl Fischer method which is well known in the art and is described in the 1990 U. S. Pharmacopoeia at pages 1619-1621, and the European Pharmacopoeia, second edition (1992), part 2, sixteenth fascicule at v. 3.5.6-1.

According to a further aspect, the present invention provides a process for the production of valaciclovir hydrochloride in anhydrous crystalline form which comprises treating valaciclovir hydrochloride with a solubilising solvent serving to convert an amount of valaciclovir hydrochloride into said anhydrous crystalline form having the d spacing pattern shown above in the first aspect of invention; and thereafter isolating said anhydrous crystalline form.

The invention also provides a process for the production of valaciclovir hydrochloride in an anhydrous crystalline form having the d spacings shown above, said process comprising the steps of.

- a) forming valaciclovir in solution either in free base or salt form;
- b) converting said free base valaciclovir or a salt thereof (when not the hydrochloride salt) to valaciclovir hydrochloride;
- c) isolating valaciclovir hydrochloride from the solution and optionally removing unbound (damp, non-solvated) solvent leaving the valaciclovir hydrochloride in substantially dry form;
- d) treating valaciclovir hydrochloride with a solubilising solvent serving to convert an amount of the optionally dried valaciclovir hydrochloride from step c) into said anhydrous crystalline form; and

e) isolating said anhydrous crystalline form.

Valaciclovir may be prepared by any method known in the art, but preferably by the methods described in the references mentioned above (US patent no. 4,957,924, European patent no. 0308,065, and Beauchamp et al, Antiviral Chemistry & Chemotherapy 303, 157-164 (1992), the disclosure of US patent no. 4,957,924 being incorporated herein by reference). Preferably the process starts from acyclovir whose synthesis is described in Schaeffer et al, Nature, 272, 583-585 (1978), UK patent no. 1,523,865 and US patent no. 4,199,574). Acyclovir is firstly esterified to its L-valine ester (valaciclovir), using an optionally protected L-valine for example carbobenzyloxy-L-valine (CBZ-L-valine) in a solvent such as pyridine or DMF in the presence of a coupling agent such as N,N'-dicyclohexylcarbodiimide, optionally in the presence of a base such as 4-dimethylaminopyridine as catalyst. Protecting groups can be removed in known manner (such as by treating with formic acid in the presence of 5% palladium on carbon) following the esterification reaction. Valaciclovir in the form of the free base or a salt of another acid (e.g. the formate) can be converted into the hydrochloride salt in conventional manner, for example by treatment with hydrochloric acid in a solvent.

The synthesis of valaciclovir hydrochloride generally leads to the formation of the compound in solution in the reaction mixture from which it may be separated and purified as a solid product. The valaciclovir hydrochloride may then optionally be dried such as by slurrying in acetone and then drying. A number of factors influence the crystalline form of the solid product and in accordance with the present invention the conditions of separation and/or subsequent processing are adjusted to produce valaciclovir hydrochloride as the anhydrous crystalline form. For example a hydrate form of valaciclovir hydrochloride can be converted to the anhydrous

crystalline form using a suitable solvent under appropriate conditions.

Such suitable solvent which is preferably a water-soluble organic solvent, should be sufficiently solubilising and be employed in an amount to allow partial solubilisation to effect the conversion and precipitation for example from hydrated crystalline form to the desired anhydrous crystalline form of valaciclovir hydrochloride. Advantageously the solvent is eventually removed by drying under vacuum. Preferably the organic solvent is an alcohol advantageously a lower alcohol containing 1 to 4 carbon atoms or a lower ketone (containing 3 to 6 carbon atoms). Most preferably the lower alcohol is ethanol or a solvent composed substantially of ethanol, for example in the form of denatured alcohol such as SVM or industrial methylated spirits. Most preferably also, the lower ketone contains water, preferably aqueous acetone such as having a water content of about 6% to about 12% by weight. Preferably the drug is slurried in the lower ketone. Our early investigations also suggest that methanol and isopropyl alcohol should also be suitable lower alcohols.

According to one particular embodiment of the invention, valaciclovir hydrochloride is formed in solution, for example in ethanol/water, obtained for example by the general method referred to above and the valaciclovir hydrochloride is isolated by partial removal of the solvent by distillation followed by precipitation, for example by addition of acetone. The valaciclovir hydrochloride (such as that isolated after step c above) can be separated at this stage in an unstable solvated form by filtration. This product which is in non-desired form can then optionally be dried and processed to the desired anhydrous crystalline form as described below.

The damp valaciclovir hydrochloride following the first isolation (as in step c above) is preferably dried; such as



-7-

by being slurried in acetone then filtered and the damp solid dried for example about 30° to about 70°C to provide substantially dry valaciclovir

hydrochloride. At this point, the valaciclovir hydrochloride may contain a high proportion of the dihydrate form which has a theoretical water of hydration content of about 9.8%.

According to a process for forming anhydrous crystalline valaciclovir hydrochloride, the substantially dry valaciclovir hydrochloride (as obtained above) is mixed with an amount of lower alcohol such as ethanol or denatured alcohol, preferably in an amount of about 15% to 40% w/w, more preferably about 17% to 30% w/w. The mixture is then heated for example from about 50°C to 70°C for several hours. Finally the product is dried under vacuum to remove residual solvent, for example at about 50°C to 70°C.

The present invention also provides the anhydrous crystalline form of valaciclovir hydrochloride (hereinafter identified as "the active compound") for use in medical therapy, e.g. in the treatment of a viral disease in an animal, e.g. a mammal such as a human. The compound is especially useful for the treatment of diseases caused by various DNA viruses, such as herpes infections, for example, herpes simplex I and 2, varicella zoster, cytomegalovirus, Epstein-Barr viruses or human herpes virus-6 (HHV-6) as well as diseases caused by hepatitis B. The active compound can also be used for the treatment of papilloma or wart virus infections and, may furthermore be administered in combination with other therapeutic agents, for example with zidovudine, to treat retroviral associated infections in particular HIV infections.

In addition to its use in human medical therapy, the active compound can be administered to other animals for treatment of viral diseases, e.g. to other mammals.

The present invention also provides a method for the treatment of a viral infection, particularly a herpes viral disease, in an animal, e.g. a mammal such as a human, which comprises administering to the animal an effective antiviral amount of the active compound.

The present invention also provides the use of the active compound in the preparation of a medicament for the treatment of a viral infection.

10

The active compound may be administered by any route appropriate to the condition to be treated, but the preferred route of administration is oral. It will be appreciated however, that the preferred route may vary with for example the condition of the recipient.

15

For each of the above-indicated utilities and indications the amounts required of the active ingredient (as above defined) will depend upon a number of factors including the severity of the condition to be treated and the identity of the recipient and will ultimately be at the discretion of the attendant physician or veterinarian. In general however, for each of these utilities and indications, a suitable effective dose will be in the range 1 to 150 mg per kilogram bodyweight of recipient per day, preferably in the range 5 to 120 mg per kilogram bodyweight per day (Unless otherwise indicated, all weights of the active ingredient are calculated with respect to the free base valaciclovir). The desired dose is preferably presented as one, two, three or four or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing about 50 to 2000 mg, preferably about 250, 500, 1000 or 2000 mg of active ingredient per unit dose form.

35

The following dosage regimes are given for guidance:

- treatment of herpes simplex virus types 1 and 2 infection:-  
total daily dose of about 1 or 2 g administered at 500 mg  
twice a day or 1 g twice a day for 5 to 10 days; suppression  
of herpes simplex virus types 1 and 2 infections:- total daily  
dose about 250 to 1 g for about one to ten years (depending  
on the patient);
- 10 treatment of varicella zoster virus infections (for example  
shingles):- total daily dose about 3 g administered at 1 g  
three times a day for seven days; suppression of  
cytomegalovirus infections:- total daily dose about 8 g  
administered at 2 g 4 times a day; for transplant patients  
15 this daily dose is administered for three to six months for  
the period at risk; and for HIV positive patients a daily dose  
is administered as usually indicated for improving quality of  
life, for example for two years or more.
- 20 Early results now indicate that valaciclovir can be used in  
the effective suppression of recurrent genital herpes at a  
once daily dose of from about 200 mg to about 1000 mg for an  
effective treatment period. The most likely daily dosages are  
250 mg, 500 mg or 1000 mg.
- 25 While it is possible for the active ingredient to be  
administered alone, it is preferable to present it as a  
pharmaceutical formulation. The formulation comprises the  
active ingredient as above defined, together with one or more  
30 pharmaceutically acceptable excipients therefor and optionally  
other therapeutic ingredients. The excipient(s) must be  
"acceptable" in the sense of being compatible with the other  
ingredients of the formulation and not deleterious to the  
recipient thereof.
- 35 The formulations include those suitable for oral administra-  
tion and may conveniently be presented in unit dosage form  
prepared by any of the methods well known in the art of  
pharmacy. Such methods include the step of bringing into  
40 association the active ingredient with the carrier which  
constitutes one or more accessory ingredients. In general,

the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

5

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, sachets of granules or tablets (such as a swallowable, dispersible or chewable tablet) each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

15

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

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Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose (as herein above recited) or an appropriate fraction thereof, of the active ingredient.

30

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include

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flavouring agents or taste masking agents.

The invention is illustrated by the following examples:

5 Example 1

A. 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl) methoxy]ethyl-N-[(benzoxo)carbonyl]-L-valinate

10 CBZ-L-valine (170 g) was dissolved in dimethylformamide (DMF) (750 ml) and cooled. A cold solution of N,N-dicyclohexyl-carbodiimide (DCC) (156.7 g) in DMF (266 ml) was added and stirred with cooling. Acyclovir (10.1 g) was added in a single portion, and then 4-(dimethylamino)pyridine (9.4 g) was  
15 added while maintaining cooling. The mixture was stirred cold overnight. A white precipitate of the by-product was then removed by filtration. The filtrate was reduced in volume by vacuum distillation and the concentrate treated with water (663 ml) then heated to 70°C. The suspension was cooled to  
20 20°C, filtered and the solid washed with water.

The damp, crude material was then purified by recrystallisation from denatured alcohol (1.2 litres) to afford the title compound as a damp white crystalline solid  
25 (281.5 g).

B. 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl) methoxy]ethyl-L-valinate hydrochloride

30 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl-N-[(benzyloxy)carbonyl]-L-valinate (175 g) was charged to aqueous denatured alcohol (335 ml/795 ml) and heated to reflux. The solution was then cooled to 40°C. The suspension was treated with 5% palladium on carbon catalyst (35 g wet weight 50% wet with water) then formic acid (30.6 ml of 90%  
35 w/w) added over 1 hour. The reaction mixture was stirred for a further 1 hour then a second charge of formic acid made

(19.5 ml) and the mixture filtered to remove the catalyst. The filter cake was washed with denatured alcohol and the combined filtrates were treated with concentrated hydrochloric acid (33.7 ml) and the resultant mixture was concentrated by vacuum distillation.

Acetone (1295 ml) was then added over 15 minutes and the suspension stirred for 1 hour before filtering off the product. The solid was then slurried with acetone (circa. 530 ml), refiltered and dried at 60°C in vacuo to give the title compound (1123 g : 81.6%).

A 15 g sample of this material was combined with denatured alcohol (circa. 7 ml), to moisten and was heated with agitation at 60°C overnight in a closed flask to avoid loss of alcohol and maintain the dampness of the mixture. The mixture was then dried at 60°C in vacuo to afford the product as the desired morphic form.

Physical Data:

Karl Fischer value : 0.9% w/w water.

The X-ray powder diffraction patterns of the product of example 1B are shown in Figure 1 of the accompanying drawings.

The d spacings and further X-ray diffraction data are shown in Table 1.

Table 1

	Peak No:	Angle (degrees)	Peak (counts)	d Spacing pattern (Å)	Error in d ( $\pm$ Å)	I/I <sub>max</sub> (%)
5	1	3.56	680	24.8	0.5	24
	2	8.62	1151	10.25	0.08	39
	3	9.42	87	9.38	0.07	3
10	4	10.86	1438	8.14	0.06	49
	5	12.10	835	7.31	0.06	28
	6	13.22	198	6.69	0.05	6
	7	14.49	2172	6.11	0.05	75
	8	15.12	455	5.85	0.03	15
15	9	15.90	352	5.57	0.02	12
	10	16.45	1969	5.38	0.02	68
	11	16.90	744	5.24	0.02	25
	12	17.33	119	5.11	0.02	4
	13	18.12	1013	4.89	0.02	35
20	14	22.71	1429	4.43	0.02	49
	15	20.55	256	4.32	0.02	8
	16	21.21	370	4.19	0.02	12
	17	21.83	753	4.07	0.02	26
	18	22.71	95	3.91	0.02	3
25	19	23.95	2893	3.71	0.02	100
	20	25.10	171	3.54	0.02	5
	21	26.21	1784	3.40	0.02	61
	22	26.89	428	3.31	0.02	14
	23	27.08	373	3.29	0.02	12
30	24	28.02	158	3.18	0.02	5
	25	28.27	161	3.15	0.02	5
	26	28.91	391	3.09	0.02	13
	27	29.68	191	3.01	0.02	6
	28	30.55	502	2.92	0.02	17
35	29	31.34	110	2.85	0.02	3
	30	31.58	98	2.83	0.02	3
	31	32.13	597	2.78	0.02	20
	32	32.96	260	2.72	0.02	8
	33	33.99	344	2.64	0.02	11
40	34	34.38	374	2.61	0.02	12
	35	35.12	141	2.55	0.02	4
	36	36.78	408	2.44	0.02	14
	37	38.71	101	2.32	0.02	3

45  $I/I_{\max} = (\text{peak height}/\text{max. peak ht}) \times 100$

The powder sample used to produce the above X-ray diffraction

data was prepared by an equivalent method as the powder sample used to produce the X-ray diffraction data of table 2 (described hereinafter) except that for the above data the following preparation was used to prepare the powder sample.

5

The sample was prepared by milling 1 g of sample in a plastic cup using two acrylic balls for 5 minutes with a Chemplex Spectromill. The samples were then back packed against a glass slide to a depth of 2 mm.

10

The X-ray diffraction scan was obtained using a Scintag PADV diffractometer in the step scan mode at  $0.02^\circ$  per step and a 10 second count per step. The sample holder was spun at 1 rotation per second during the scan. Additional setting as described below.

15

X-ray generator: 45 kV, 40 mA  
Radiation: Copper K alpha radiation  
Fixed divergent slit: 1 mm  
Incident scatter slit: 2 mm  
Diffracted scatter slit: 0.5 mm  
Receiving slit: 0.3 mm  
Goniometer radius: 235 mm  
Detector: Scintillation with a graphite monochromator.

25

The peak intensities are reported as absolute counts of the peak top. The intensity units on the X-ray diffraction plot are counts/sec. The absolute counts = counts/sec x count time = counts/sec x 10 sec. The peak intensities in the table have been corrected for background and copper K alpha II X-ray wavelength contribution.

30

Slight variations in d spacings are expected based on the specific diffractometer employed and the analyst's sample preparation technique. More variation is expected for the relative peak intensities. Identification of the exact crystal form of a drug should be based primarily on observed

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d spacings with lesser importance placed on relative peak intensities. To identify the anhydrate crystal form of valaciclovir hydrochloride, the fifteen most intense diffraction peaks are reasonably characteristic. These peaks occur at  $10.25 \pm 0.08$ ,  $8.14 \pm 0.06$ ,  $7.31 \pm 0.06$ ,  $6.11 \pm 0.05$ ,  $5.85 \pm 0.03$ ,  $5.38 \pm 0.02$ ,  $5.24 \pm 0.02$ ,  $4.89 \pm 0.02$ ,  $4.43 \pm 0.02$ ,  $4.07 \pm 0.02$ ,  $3.71 \pm 0.02$ ,  $3.40 \pm 0.02$ ,  $3.31 \pm 0.02$ ,  $2.92 \pm 0.02$ , and  $2.78 \pm 0.02$  angstroms. The error in determining d spacings decrease with increasing diffraction scan angle or decreasing d spacing. The error of the 10.25 angstroms peak would be approximately  $\pm 0.08$  angstrom and the error of the 2.78 angstroms peak would be approximately  $\pm 0.01$  angstrom for a reasonably aligned diffractometer and reasonably prepared sample.

The first peak in the line listing at 3.56 degrees is due to a hydrated crystal phase of valaciclovir hydrochloride and not due to the anhydrate crystal form.

In a further sample of anhydrous crystalline valaciclovir hydrochloride, the following d spacings were obtained:

10.20, 8.10, 7.27, 6.68, 6.08, 5.83, 5.56, 5.37, 5.23, 5.10, 4.89, 4.42, 4.31, 4.18, 4.06, 3.91, 3.71, 3.64, 3.54, 3.39, 3.35, 3.32, 3.28, 3.22, 3.18, 3.14, 3.08, 3.00, 2.97, 2.91, 2.85, 2.77, 2.70, 2.63, 2.60, 2.55, 2.44, 2.42, 2.37, 2.32.

The fifteen most characteristic peaks are  $10.20 \pm 0.08$ ,  $8.10 \pm 0.05$ ,  $7.27 \pm 0.04$ ,  $6.08 \pm 0.03$ ,  $5.83 \pm 0.03$ ,  $5.37 \pm 0.02$ ,  $5.23 \pm 0.02$ ,  $4.89 \pm 0.02$ ,  $4.42 \pm 0.02$ ,  $4.06 \pm 0.01$ ,  $3.71 \pm 0.01$ ,  $3.39 \pm 0.01$ ,  $3.32 \pm 0.01$ ,  $2.9 \pm 0.01$ , and  $2.77 \pm 0.01$ .

Example 2A. 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl) methoxy]ethyl-N-[(benzyloxy)carbonyl]-L-valinate

5

CBZ-L-valine (167 g) was dissolved in dimethylformamide (DMF) (750 ml) and cooled. A cold solution of N,N-dicyclohexylcarbodiimide (DCC) (153.5 g) in DMF (266 ml) was added followed by acyclovir (111.7 g) in a single portion. 4-(dimethyl-amino)pyridine (9.4 g) was then added and the mixture stirred cold overnight. A white precipitate of the by-product was then removed by filtration. The filtrate was reduced in volume as before to give the title compound (215.3 g).

15

B. 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl) methoxy]ethyl-L-valinate hydrochloride

2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl-N-[(benzyloxy)carbonyl]-L-valinate (200 g) was charged to aqueous denatured alcohol (382 ml/908 ml) and heated to reflux to dissolve solids. The solution was then cooled to 40°C. The suspension was treated with a 50% w/w paste of 5% palladium on carbon catalyst and water (40 g) then formic acid (96% w/w : 32.8 ml) added over 1 hour. The reaction mixture was stirred for a further 1 hour then a second charge of formic acid made (20.88 ml) and the mixture filtered to remove the catalyst. The filtrate was treated with concentrated hydrochloric acid (38.56 ml) and the resultant mixture distilled and concentrated under vacuum.

30

Acetone (1480 ml) was then added over 15 minutes and the suspension stirred for 1 hour before filtering off the product. The solid was then slurried with acetone (ca. 500 ml), refiltered and dried at 60°C in vacuo to give the title compound (137.75 g : 87.6%).

35

A 10 g sample of this material was combined with denatured alcohol (3.5 ml), heated at 60°C for several hours and the solvent then removed in vacuo to afford the product as the desired morphic form.

5

Result: Valaciclovir hydrochloride in the anhydrous crystalline form was obtained substantially free of other forms of valaciclovir hydrochloride (i.e. in more than about 90% w/w anhydrous crystal form purity).

10

Physical Data:

The X-ray powder diffraction patterns of the product of example 1B are shown in Figures 2 and 3 of the accompanying drawings in which:-

15

Fig 2 is a linear plot X-ray diffractogram; and

Fig 3 is a square root plot X-ray diffractogram.

20

The d spacings and further X-ray diffraction data are shown in Table 2.

Table 2

25

	Peak No:	Angle (degrees)	Peak (counts)	d Spacing pattern (Å)	I/Imax (%)
30	1	3.62	2673	24.40	35
	2	7.21	119	12.26	2
	3	8.64	1910	10.22	25
	4	9.43	180	9.37	2
	5	10.86	2652	8.14	35
35	6	12.12	734	7.30	10
	7	13.24	615	6.68	8
	8	13.77	106	6.42	1
	9	14.50	2333	6.11	31
	10	15.14	635	5.85	8
40	11	15.89	511	5.57	7
	12	16.44	2652	5.39	35

Table 2 - continued

	Peak No:	Angle (degrees)	Peak (counts)	d Spacing pattern (Å)	I/I <sub>max</sub> (%)
5	13	16.90	1267	5.24	17
	14	17.33	475	5.11	6
	15	18.13	1648	4.89	22
10	16	20.05	2172	4.43	28
	17	20.56	640	4.32	8
	18	21.20	1096	4.19	14
	19	21.78	2034	4.08	27
	20	21.90	1384	4.06	18
15	21	22.66	729	3.92	10
	22	23.94	7621	3.71	100
	23	24.39	1624	3.65	21
	24	25.11	967	3.54	13
	25	25.86	2460	3.44	32
20	26	26.21	5127	3.40	67
	27	26.82	1892	3.32	25
	28	26.89	1927	3.31	25
	29	27.19	1429	3.28	19
	30	27.99	1156	3.18	15
25	31	28.35	1076	3.15	14
	32	28.87	1722	3.09	23
	33	28.94	1529	3.08	20
	34	29.62	1274	3.01	17
	35	30.56	1673	2.92	22
30	36	31.30	999	2.86	13
	37	32.25	2570	2.77	34
	38	33.04	1376	2.71	18
	39	34.00	1806	2.63	24
	40	34.45	1225	2.60	16
35	41	35.13	1149	2.55	15
	42	36.77	1600	2.44	21
	43	38.01	576	2.37	8
	44	38.76	729	2.32	10
	45	39.52	524	2.28	7
40	46	40.70	751	2.22	10
	47	41.28	870	2.19	11
	48	41.88	686	2.16	9
	49	42.47	718	2.13	9
	50	43.40	548	2.08	7
45	51	44.53	729	2.03	10

The diffraction patterns of the product of example 2B were generated on a Phillips PW1800 Automatic X-ray Powder Diffractometer using a scan of 2 to 45 2θ with step intervals

of 0.02 degrees and an integration time of 4 seconds per step.

Generator settings: 40 KV, 45 mA, Cu alpha 1,2 wavelengths:  
1.54060, 1.54439 Å; Step size, sample time: 0.020 deg, 4.00  
5 s, 0.005 deg/s; monochromator used: yes; divergence slit:  
automatic (irradiated sample length: 10.0 mm); peak angle  
range: 2.000 - 45.000 deg; range in D spacing: 44.1372 -  
2.01289 Å; peak position criterion: top of smoothed data;  
cryst peak width range: 0.00 - 2.00 deg; minimum peak  
10 significance: 0.75 maximum intensity: 7621 cts, 1905.3 cps.

The powder sample was prepared as follows:

15 A 1 gram portion of valaciclovir hydrochloride was transferred  
to a Retsch 10 ml polystyrol container ref 31-762 containing  
2 acrylic balls ref 26-253 and was then ground to a very fine  
powder using a Retsch MM2 miser mill set at 100% power for  
five minutes. The ground powder was back loaded into a  
20 Philips PW1811/10 sample holder which had been placed inverted  
on a perfectly smooth surface (e.g. that afforded by a glass  
plate or a highly polished metal sheet). The powder was then  
packed into the holder and further powder added and packed  
until the holder was full. A Philips PW 1811 00 bottom plate  
25 was then clamped into the holder and the entire assembly was  
then inverted before removing the glass/metal plate in an  
upwards direction to reveal the smooth sample surface which  
was flush with that of the holder.

30 As illustrated above, crystalline forms of valaciclovir  
hydrochloride can be characterised by their X-ray powder  
diffraction pattern. Figures 1 to 3 show diffractograms of  
the anhydrous crystalline form of valaciclovir hydrochloride  
as a linear plot (Figures 1 and 2) and a square root plot  
(Figure 3). In each case the diffractogram displays count  
35 rate (intensity of the diffracted peak) against diffraction  
angle  $2\theta$ . The linear plot allows easy rationing of the peak  
intensifies whereas the square root plot attenuates small

peaks thereby emphasising the main peaks in the diffraction pattern.

Example 3

5

Hygroscopicity and Stability Measurements of anhydrous Crystalline Valaciclovir Hydrochloride

10 Hygroscopicity: An integrated microbalance system was used to measure equilibrium water sorption profiles (Model MB300G, VTI Corp.), weighing about 20 mg of valaciclovir hydrochloride, and using the following conditions:

Drying parameters:-

15 Temperature: 65°C; heating rate: 10°C/min; equilibrium criteria: 5 µg; sample interval: 5 min

Sorption parameters:-

Temperature: 25°C; equilibrium criteria: 5 µg; sample interval: 5 min.

Data Collection Interval: 2 min

20

The water sorption/desorption were isotherms noted in Figure 4.

25 The isotherm shows that only a small amount of water is absorbed. This absorption is, in fact, due to the presence of hydrated crystal form in the sample which is consistent with the 0.9% w/w water measured by the Karl Fischer titration.

30 The effect of the small amount of this hydrate can be seen more clearly by comparing with the isotherm of figure 5 which was generated with substantially 100% anhydrate crystal form.

35 X-ray powder diffraction: No change between the initial powder pattern and the patterns of material stored for 4 weeks at 40°C, ambient temp/60% RH (relative humidity), and 40°C/75%

RH.

% water :

	Initial:	0.9
5	40°C 2 weeks:	0.8
	40°C 4 weeks:	0.8
	ambient T/60% RH, 2 weeks:	1.0
	ambient T/60% RH, 4 weeks:	0.9
	40°C/75% RH, 2 weeks:	1.1
10	40°C/75% RH, 4 weeks:	1.1

Four weeks chemical bulk stability data:

% w/w on anhydrous basis

15		INITIAL	40°C	ambient T/60% RH	40°C/ 75%RH
	L-valine:	ND (< 0.1%)	ND	ND	ND
20	2-hydroxyethyl valinate hydrochloride:	ND (< 0.1%)	ND	ND	ND
	Acyclovir:	0.9	0.9	0.9	0.9
	Guanine:	ND (< 0.1%)	ND	ND	ND
	D-isomer of				
25	valaciclovir:	1.1	1.2*	1.1	1.2*
	Valaciclovir HCl:	97.3	97.8	98.2	97.5

ND = none detected

Data rounded to nearest 1.1% w/w

\*There is no significant increase in 2-hydroxyethyl valinate hydrochloride; the actual values between the initial and 4 week time points are within 0.03% of each other (which is within experimental error).

Example 4

Further hygroscopicity and stability studies were carried out on substantially 100% anhydrate crystal form at 30°C/75% RH (12 months) and 40°C/75% RH (6 months).

Samples stored at 30°C/75% RH and 40°C/75% for 12 months and 6 months, respectively, showed no significant change in moisture content (Karl Fischer) or crystallinity (as measured by X-ray powder diffraction). Using the integrated microbalance system, no more than 0.5% w/w water is absorbed at 25°C at relative humidities of up to 90%. Furthermore, a separate sample stored for 2.5 months at 25°C and 75% RH corroborated the moisture content measured by the integrated microbalance system, that is, about 0.3% moisture at 75% RH.

The results indicate that the anhydrous crystalline form of valaciclovir hydrochloride is chemically and physically stable.

These characteristics give the anhydrous crystalline form good formulation and storage properties, and assist in obtaining in a highly reproducible manner, batches of high crystalline form purity.



**Example 5: Tablet Formulation**

The following formulations was prepared as follows using anhydrous crystalline valaciclovir.

5

10

15

Example	5		Per Batch (kg)
Ingredients	mg/ tablet	w/w	
valaciclovir hydrochloride*	615	65.74	5.289
lactose	205	21.91	1.763
microcrystalline cellulose (Avicel PH101) (intragranular)	75	8.02	0.6450
povidone k30	18	1.92	0.1548
crospovidone (intragranular)	18	1.92	0.1548
colloidal silicon dioxide (Aerosil 200)	0.9	0.10	0.002598
magnesium stearate	3.6	0.38	0.03096
TOTAL WEIGHT	935.5	100	

20

\*bulk density 0.45 g/cc after 50 taps (anhydrous crystalline form)

**Example 6: Tablet Formulation**

The following formulations was prepared as follows using anhydrous crystalline valaciclovir.

5

Example	6		Per Batch (kg)
	mg/ tablet	w/w	
<b>Ingredients</b>			
valaciclovir hydrochloride*	576.5	82.3	0.9973
10 crosopovidone (intragranular)	14.0	2.0	0.02422
povidone k90 (intragranular)	14.0	3.1	0.03806
crosopovidone (extragranular)	14.0	2.0	0.11200
microcrystalline cellulose (Avicel PH101) (extragranular)	70.0	10.0	0.05600
15 colloidal silicon dioxide (CAB-O-SIL M-50) (extragranular)	2.0	0.3	0.00160
magnesium stearate (extragranular)	4.0	0.6	0.00320
20 TOTAL WEIGHT	702.5	100.0	1.13158

\*bulk density 0.60 g/cc after 50 taps (anhydrous crystalline form); Karl Fischer water content = 0.4.

25

Tablet Preparation For Example 5:

Step 1. The following ingredients as shown were sifted with a hand screen as shown.

5

30 Mesh  
valaciclovir hydrochloride  
lactose  
microcrystalline cellulose  
povidone K30  
crospovidone

10

15

60 Mesh  
magnesium stearate  
colloidal silicon dioxide (CSD)

Step 2. The 30 mesh sifted ingredients from Step 1 were then blended, excluding the povidone, in a 1 cubic foot V-shell blender for 10 minutes.

20

Step 3. 1.540 kg of SD3A alcohol (ethanol denatured with 5% methanol) was then mixed with 0.6600 kg of purified water and the screened povidone, 0.1548 kg, was dissolved in 0.6192 kg of the mixed solvents by hand stirring.

25

Step 4. The blended powders from Step 2 were then granulated in a 1 cubic foot Littleford Lodige mixer by adding the dissolved povidone while mixing. 1.315 kg of more mixed solvent was added and the mixture massed for seven minutes total as shown below.

30

Ploughs 7 min                      Choppers 6.5 min

35

Step 5. The granule from Step 4 was then dried in a Fluid Bed Dryer (Glatt GPCG5) with an inlet air temperature of 50°C to any acceptable moisture content of approximately 1.0 to 3.0% L.O.D.

5

Step 6. The material from Step 5 was then sifted using a Fitz Mill Model M fitted with a 30 mesh screen, with knives forward, operating at medium speed.

10

Step 7. The screened a magnesium stearate from Step 1, was added to the material from Step 6 and blended for 5 minutes using the blender from Step 2.

15

Step 8. Lubricated granule 2.650 kg (from Step 7) was weighed and the sifted CSD, from Step 1, added then dispersed by hand and the mixture blended for 5 minutes in the blender from Step 2. The mixture was compressed to form tablets on a Manesty Beta Press fitted with oval tooling, 19.1 mm x 10.2 mm, at a compression weight of approximately 935.5 mg.

20

Tablet Preparation For Example 6:

- 5      Step 1.      The core ingredients were sifted with a 20 mesh hand screen, and then blended in an appropriately sized V-shell blender for 10 minutes.
- 10      Step 2.      The blended powders from Step 1 were then granulated in a 10 litre high shear mixer (model-SP1) by adding pure water while mixing. Approximately 11-14% water, w/w of the core ingredients was then added and the mixture massed for 3 to 4½ minutes.
- 15      Step 3.      The granule from Step 2 was dried in a tray (examples 5, 6 and 7) or vacuum (examples 3 and 4) drier (model-SP1) at a temperature of 50°C to an acceptable moisture content of approximately 1.0 to 2.0 % L.O.D.
- 20      Step 4.      The remaining ingredients were sifted through a 20 mesh screen and added to the core ingredients of step 3, and then the mixture was sifted using a Comil Model 197 AS fitted with a 0.062" screen.
- 25      Step 5.      The mixture was then blended in an appropriately sized V-shell blender for 5 minutes.
- 30      Step 6      The blended granule from Step 5 was compressed on a Manesty Beta Press fitted with capsule shaped tooling, 18.25 mm x 7.14 mm, at a compression weight of approximately 700 mg and a compression force of about 14.5 to 18 kN.
- 35      Step 7      The tablet can then, optionally be film coated using standard methods such as using white colour concentrate, methylhydroxypropylcellulose, titanium dioxide, polyethylene glycol and polysorbate.

CLAIMS

1. Valaciclovir hydrochloride in essentially anhydrous  
5 crystalline form including substantially the following  
d spacing pattern (in Angstroms):  
  
10.20  $\pm$  0.08, 8.10  $\pm$  0.06, 7.27  $\pm$  0.06, 6.08  $\pm$  0.05,  
5.83  $\pm$  0.03, 5.37  $\pm$  0.02, 5.23  $\pm$  0.02, 4.89  $\pm$  0.02, 4.42  
10  $\pm$  0.02, 4.06  $\pm$  0.02, 3.71  $\pm$  0.02, 3.39  $\pm$  0.02, 3.32  $\pm$   
0.02, 2.91  $\pm$  0.02, 2.77  $\pm$  0.02.
2. Crystalline valaciclovir hydrochloride as claimed in  
claim 1 having a water of hydration content of not more  
15 than 3% w/w.
3. Crystalline valaciclovir hydrochloride as claimed in  
claim 2 having a water of hydration content of not more  
than 2% w/w.  
20
4. Crystalline valaciclovir hydrochloride as claimed in  
claim 3 having a water of hydration content of not more  
than 1% w/w.
- 25 5. Crystalline valaciclovir hydrochloride having  
substantially the same X-ray diffraction pattern as  
shown in Figures 1 to 3.
6. Crystalline valaciclovir hydrochloride as claimed in any  
30 one the preceding claims for use in medical therapy.
7. Use of valaciclovir hydrochloride as claimed in any one  
of claims 1 to 5 in the preparation of a medicament for  
the treatment of a herpes viral infection.  
35
8. A method for the treatment of herpes viral infection in

a human which comprises administering to the human host, an effective anti-herpes viral amount of crystalline valaciclovir hydrochloride as claimed in any one of claims 1 to 5.

5

9. A process for the production of valaciclovir hydrochloride in anhydrous crystalline form including substantially the d spacings as defined in claim 1, said process comprising treating valaciclovir hydrochloride with an amount of solubilising solvent serving to convert an amount of said valaciclovir hydrochloride into said anhydrous crystalline form; and then isolating said anhydrous crystalline form.

10

- 15 10. A process for the production of valaciclovir hydrochloride in an anhydrous crystalline form including substantially the d spacings as defined in claim 1, said process comprising the steps of:

20

a) forming valaciclovir in solution either in free base or salt form;

b) converting said free base valaciclovir or salt thereof to valaciclovir hydrochloride;

25

c) isolating valaciclovir hydrochloride from the solution and optionally removing unbound solvent leaving the valaciclovir hydrochloride in substantially dry form;

30

d) treating valaciclovir hydrochloride with a solubilising solvent serving to convert an amount of said optionally dried valaciclovir hydrochloride into said anhydrous crystalline form; and

e) isolating said anhydrous crystalline form.

35

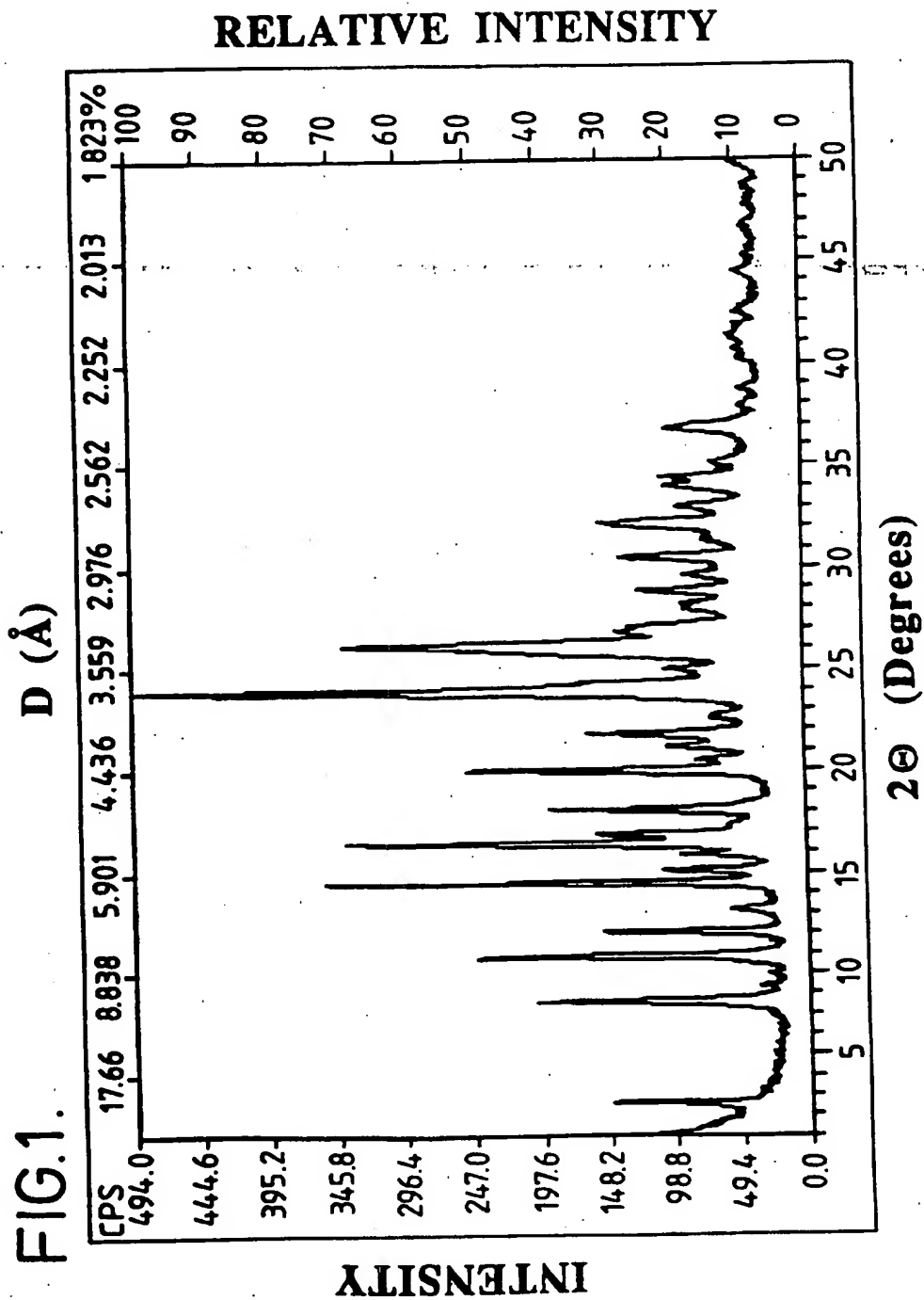
11. A process as claimed in claim 10 wherein the solubilising solvent is a lower alcohol having 1 to 4

carbon atoms.

- 5        12. A process as claimed in claim 11 wherein the lower alcohol is ethanol or a solvent composed substantially of ethanol.
- 10       13. A process as claimed in claim 12 wherein the lower alcohol is ethanol or a solvent composed substantially of ethanol and is added in a range of about 17% by weight to about 40% by weight of substantially dry valaciclovir hydrochloride.
- 15       14. A process as claimed in claim 10 wherein the solubilising solvent is a lower ketone containing from 3 to 6 carbon atoms.

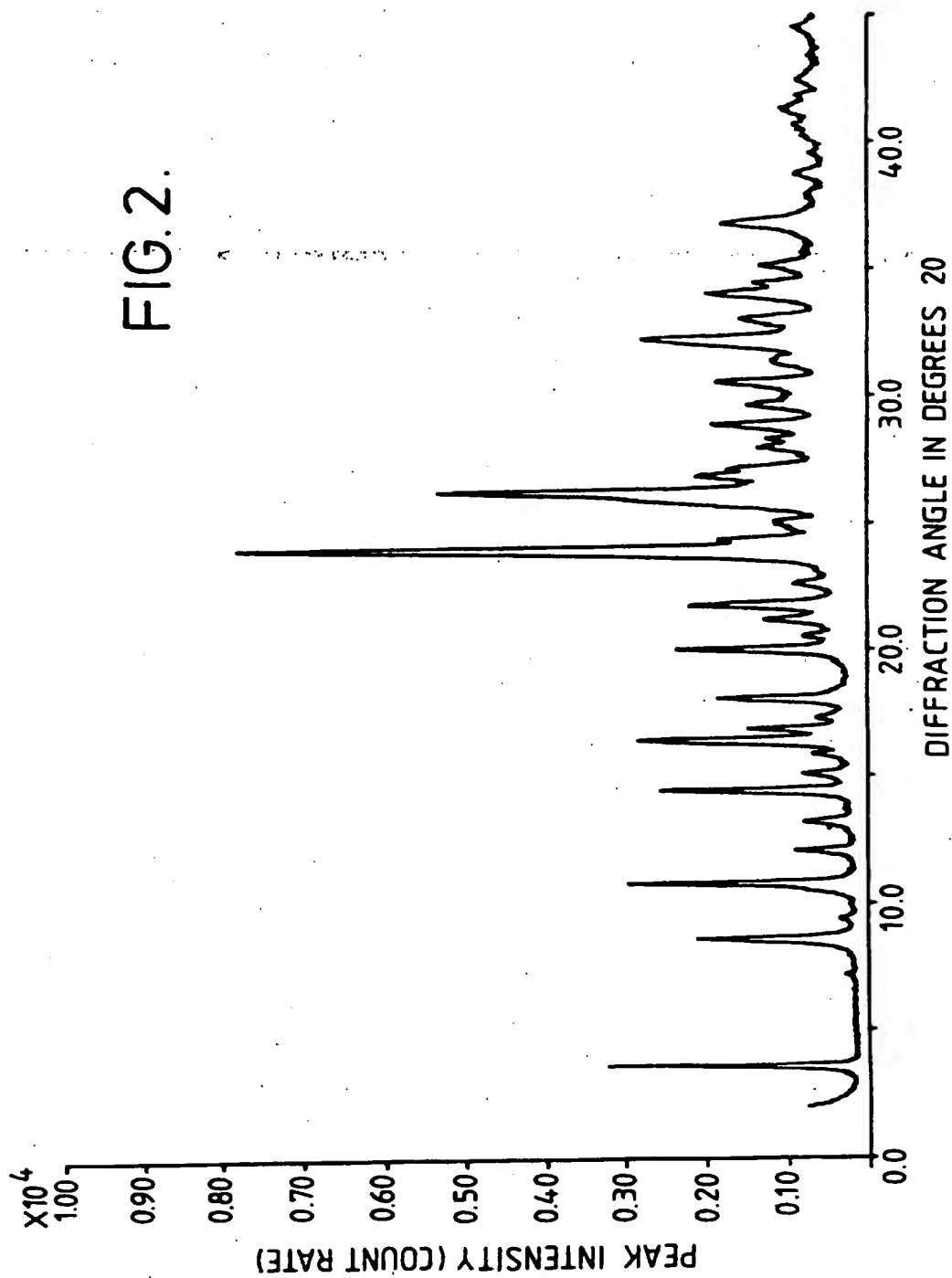


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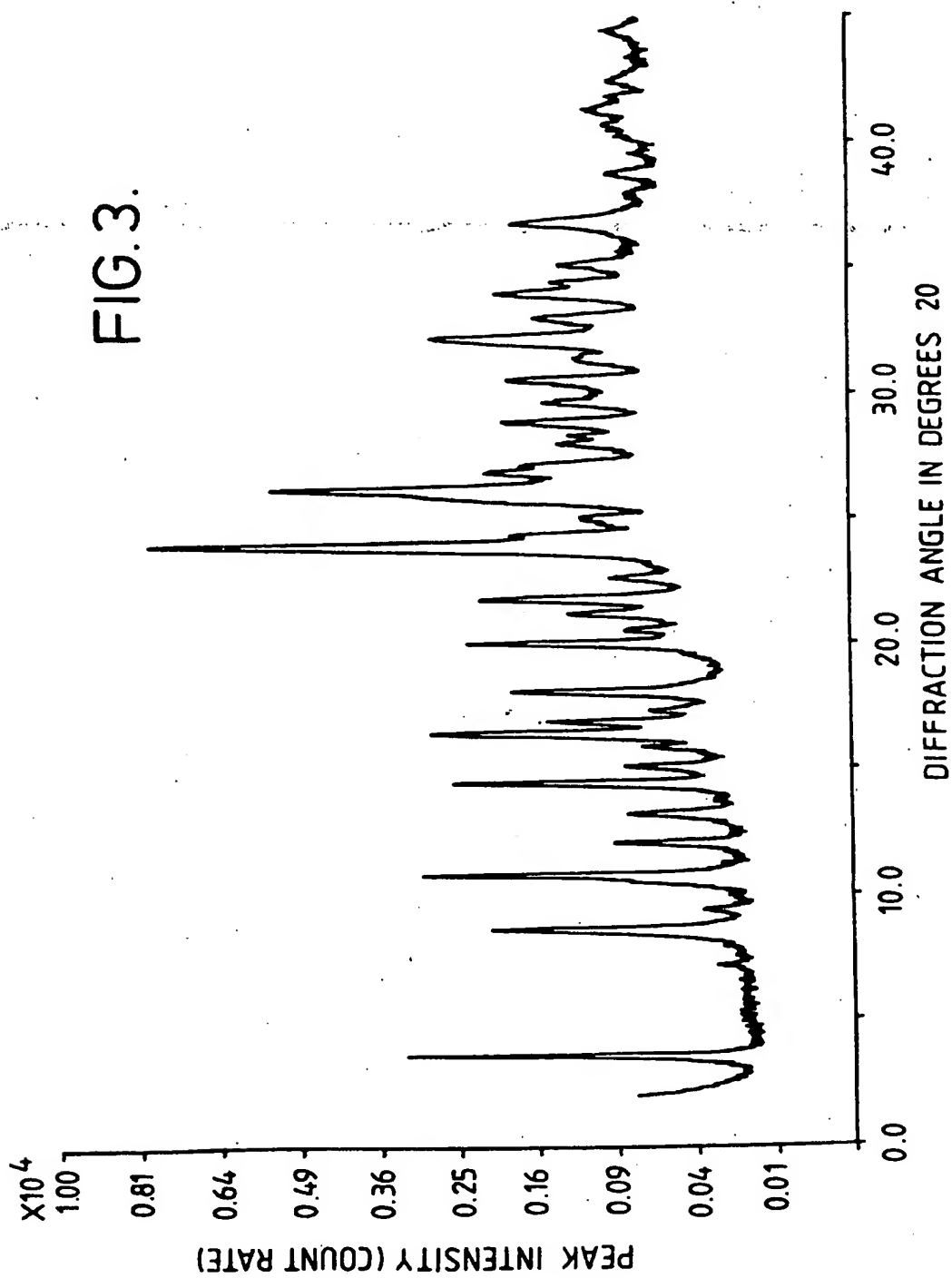


2/4

FIG. 2.



3/4



4/4

FIG.4

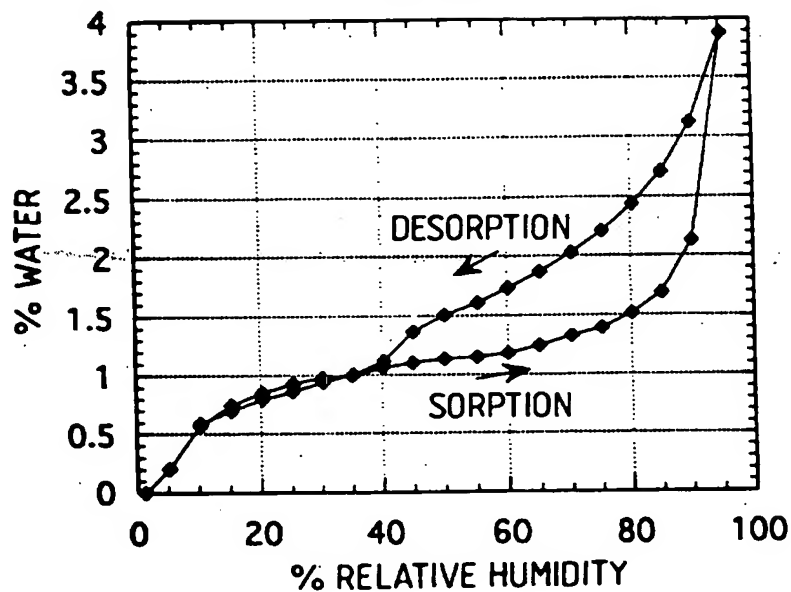
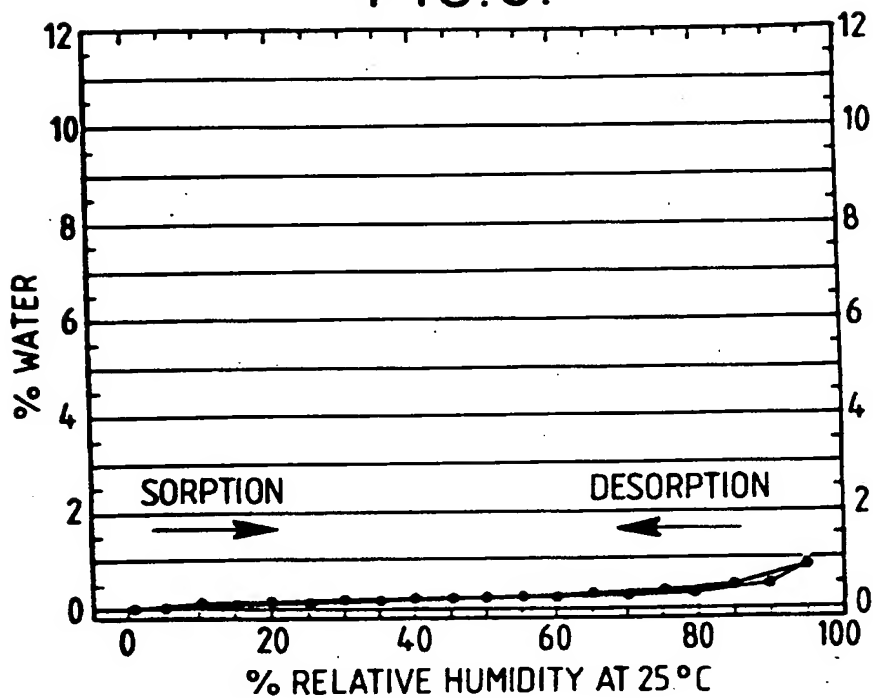


FIG.5.



# INTERNATIONAL SEARCH REPORT

Internal. Application No

PCT/GB 96/00117

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 C07D473/00 A61K31/52

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 596 542 (THE WELLCOME FOUNDATION LIMITED) 11 May 1994 see page 7-8; examples 1B-1D ---	1
A	WO,A,94 29311 (FARMHISPANIA SA) 22 December 1994 see page 1-8; examples 1-4 ---	1
A	EP,A,0 308 065 (THE WELLCOME FOUNDATION LIMITED) 22 March 1989 cited in the application see page 7-9; examples 1B-1D --- -/--	1



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family.

Date of the actual completion of the international search

15 April 1996

Date of mailing of the international search report

26.04.96

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# INTERNATIONAL SEARCH REPORT

Internal Application No  
PCT/GB 96/00117

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>ANTIVIRAL CHEMISTRY &amp; CHEMOTHERAPY, vol. 3, no. 3, 1992, pages 157-164, XP002000503 L.M. BEAUCHAMP ET AL: cited in the application see page 162, left-hand column -----</p>	1

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Internat. Application No

PCT/GB 96/00117

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		DE-D- 3852682	16-02-95
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		JP-A- 1068373	14-03-89
		JP-B- 6062623	17-08-94
		JP-A- 3115284	16-05-91
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		US-A- 4957924	18-09-90
		US-A- 5061708	29-10-91
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